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(54) DRUGS FOR AMELIORATING PULMONARY CIRCULATION

(57) A pulmonary circulation improving agent contains a prostaglandin I derivative as an active component, and has the vasodilating action selective to the pulmonary blood vessels. The agent has the effect of improving pulmonary circulation by administration to a patient suffering from the increased pulmonary vascular resistance.

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Descripti n

Technical Field

[0001] The present invention relates to a pulmonary circulation improving agent containing as an active component a prostaglandin I derivative or a salt thereof, and a pulmonary circulation improving method using the agent.

Background Art

[0002] Vasodilators have selectivity to the blood vessels depending upon the types thereof, and for example, a Ca antagonist such as nifedipine or the like, a nitrate agent such as nitroglycerin or the like are known to be highly selective to the coronary artery. However, conventional vasodilators are low selective to the pulmonary blood vessels. It has been reported that, for example, the use for treating pulmonary hypertension causes adverse effects due to a decrease in the systemic blood pressure.

[0003] On the other hand, prostaglandin I_2 (PGI_2, prostacyclin) (refer to "Nature" Vol. 268, p. 688, 1976) which is representative of prostaglandin I derivatives is known as a substance having the strong action to inhibit platelet aggregation and the strong action to dilate the peripheral artery. As compounds in which the instability of PGI_2 is significantly improved, Japanese Examined Patent Publication Nos. 2-12226, 2-57548 and 1-53672 disclose PGI_2 derivatives having a skeleton in which the structure of the exoenol ether moiety, which is the characteristic structure of PGI_2, is converted into the inter-m-phenylene type. As other compounds in which the stability of prostaglandin I is improved, ataprost, iloprost, clinprost, ciprostene, naxaprostene, taprostene, cicaprost, pimilprost, CH-169, and CS570 are known [refer to Gendaiiryo-sha, "Review Prostaglandins" No. 1, p. 123 (1994), "New Drugs of Tomorrow" 15-IV-p. 185 (1996), and "New Drugs of Tomorrow" 15-III-p. 551 (1996)]. However, it has been not known yet that these prostaglandin I derivatives have a vasodilating action selective to the pulmonary blood vessels.

[0004] As described above, conventional vasodilators are low selective to the pulmonary blood vessels, and it has been reported that the use for treating a patient suffering from the increased pulmonary vascular resistance causes adverse effects such as a headache, emesis, reflex tachycardia, the worsening of right heart failure, and the like.

[0005] An object of the present invention is to provide a pulmonary circulation improving agent having less adverse effects and excellent effectiveness and practicability, and a pulmonary circulation improving method.

Disclosure of Invention

[0006] The present invention provides a pulmonary circulation improving agent containing as an active component a prostaglandin I derivative, particularly, a prostaglandin I_2 derivative, and a pulmonary circulation improving method using the agent.

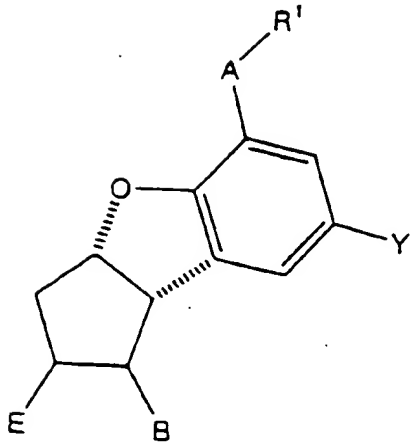
Brief Description of the Drawings

[0007]

Fig. 1 shows the results of changes in the pulmonary arterial pressure/systemic blood pressure ratio in Example 1.
Fig. 2 shows the results of changes in the pulmonary vascular resistance/systemic vascular resistance ratio in Example 1.

Best Mode for Carrying Out the Invention

[0008] As the prostaglandin I derivatives of the present invention, prostaglandin I_1 derivatives, prostaglandin I_2 derivatives, prostaglandin I_3 derivatives, or salts thereof may be used. However, prostaglandin I_2 derivatives and salts thereof are preferably used. More preferably, 4,8-inter-m-phenyleneprostaglandin I_2 derivatives or pharmacologically acceptable salts thereof represented by the following formula (I) are used.



(I)

[wherein R^1 is the following:

(A) $COOR^2$ wherein R^2 is:

1) hydrogen or pharmacologically acceptable cation;
2) straight chain alkyl having 1 to 12 carbon atoms or branched alkyl having 3 to 14 carbon atoms;
3) $-Z-R^3$
wherein Z is a valence bond or straight chain or branched alkylene represented by C_tH_{2t} wherein t represents an integer of 1 to 6, and R^3 is cycloalkyl having 3 to 12 carbon atoms or substituted cycloalkyl having 3 to 12 carbon atoms and substituted by R^4 which is hydrogen or alkyl having 1 to 5 carbon atoms;
4) $-(CH_2CH_2O)_nCH_3$
wherein n is an integer of 1 to 5;
5) $-Z-Ar^1$
wherein Z is defined as the same as the above, and Ar^1 is phenyl, α-naphthyl, β-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, α-furyl, β-furyl, α-thienyl, β-thienyl or substituted phenyl (wherein the substituent is at least one chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl, phenoxy, p-acetoamidobenzamido, $-CH=N-NH-C(=O)-NH_2$, $-NH-C(=O)-Ph$, $-NH-C(=O)-CH_3$ or $-NH-C(=O)-NH_2$);
6) $-C_tH_{2t}COOR^4$
wherein C_tH_{2t} and R^4 are defined as the same as the above;
7) $-C_tH_{2t}N(R^4)_2$
wherein C_tH_{2t} and R^4 are defined as the same as the above;
8) $-CH(R^5)-C(=O)-R^6$
wherein R^5 is hydrogen or benzoyl, and R^6 is phenyl, p-bromophenyl, p-chlorophenyl, p-biphenyl, p-nitrophenyl, p-benzamidophenyl, or 2-naphthyl;
9) $-C_pH_{2p}-W-R^7$
wherein W is $-CH=CH-$, $-CH=CR^7$ or $-C\equiv C-$, and R^7 is hydrogen or straight chain or branched alkyl or aralkyl having 1 to 30 carbon atoms, and p is an integer of 1 to 5; or
10) $-CH(CH_2OR^8)_2$
wherein R^8 is alkyl or acyl having 1 to 30 carbon atoms;

(B) $-CH_2OH$;
(C) $-C(=O)N(R^9)_2$
wherein R^9 is hydrogen, straight chain alkyl having 1 to 12 carbon atoms, branched alkyl having 3 to 12 carbon atoms, cycloalkyl having 3 to 12 carbon atoms, cycloalkylalkylene having 4 to 13 carbon atoms, phenyl, substituted phenyl (wherein the substituent is defined as the same as the above in (A) 5)), aralkyl having 7 to 12 carbon atoms, or $-SO_2R^{10}$ wherein R^{10} is alkyl having 1 to 10 carbon atoms, cycloalkyl having 3 to 12 carbon atoms, phenyl, substituted phenyl (the substitutent is defined as the same as the above in (A) 5)), or aralkyl having 7 to 12 carbon atoms, two R^9 groups may be the same or different, and when one of the R^9 groups is $-SO_2R^{10}$, the other R^9 is not

$-SO_2R^{10}$; or
(D) $-CH_2OTHP$ (THP is a tetrahydropyranyl group);

A is the following:

1) $-(CH_2)_m-$;
2) $-CH=CH-CH_2-$;
3) $-CH_2-CH=CH-$;
4) $-CH_2-O-CH_2-$;
5) $-CH=CH-$;
6) $-O-CH_2-$; or
7) $-C\equiv C-$;
wherein m represents an integer of 1 to 3;

Y is hydrogen, alkyl having 1 to 4 carbon atoms, chlorine, bromine, fluorine, formyl, methoxy or nitro;
B is $-X-C(R^{11})(R^{12})OR^{13}$
wherein R^{11} is hydrogen, alkyl having 1 to 4 carbon atoms; R^{13} is hydrogen, acyl having 1 to 14 carbon atoms, aroyl having 6 to 15 carbon atoms, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, or t-butyl; X is the following:

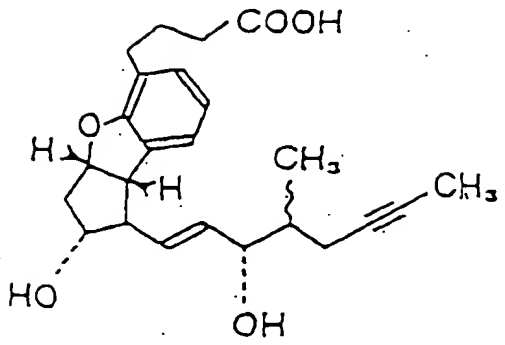
1) $-CH_2-CH_2-$;
2) $-CH=CH-$;
3) $-C\equiv C-$; and

R^{12} is the following:

1) straight chain alkyl having 1 to 12 carbon atoms, or branched alkyl having 3 to 14 carbon atoms;
2) $-Z-Ar^2$
wherein Z is the defined as the same as the above, and Ar^2 represents phenyl, α-naphthyl, β-naphthyl, or phenyl substituted by at least one chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy;
3) $-C_tH_{2t}OR^{14}$
wherein C_tH_{2t} is defined as the same as the above, and R^{14} represents straight chain alkyl having 1 to 6 carbon atoms, branched alkyl having 3 to 6 carbon atoms, phenyl, phenyl substituted by at last one chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy, cyclopentyl, cyclohexyl, or cyclopentyl or cyclohexyl substituted by 1 to 4 straight chain alkyl groups having 1 to 4 carbon atoms;
4) $-Z-R^3$
wherein Z and R^3 are defined as the same as the above;
5) $-C_tH_{2t}-CH=C(R^{15})R^{16}$
wherein C_tH_{2t} is defined as the same as the above, and R^{15} and R^{16} each represent hydrogen, methyl, ethyl, propyl, or butyl; or
6) $-C_uH_{2u}-C\equiv C-R^{17}$
wherein u is an integer of 1 to 7. C_uH_{2u} represents straight chain or branched alkylene, and R^{17} represents straight chain alkyl having 1 to 6 carbon atoms;

E is hydrogen or $-OR^{18}$
wherein R^{18} represents acyl having 1 to 12 carbon atoms, aroyl having 7 to 15 carbon atoms, or R^2 (wherein R^2 is defined as the same as the above); and
the formula represents the d, l or dl form].

[0009] Preferable examples of prostaglandin I derivatives of the present invention include beraprost or salts thereof represented by the following formula (I).



ataprost, iloprost, clinprost, ciprostene, naxaprostene, taprostene, cicaprost, pimilprost, CH-169, CS570, and the like. However, the derivatives are not limited to these compounds.

[0010] The prostaglandin I derivatives of the present invention can be synthesized by a known method. For example, compounds represented by formula (I) or salts thereof can be synthesized by the method disclosed in Japanese Examined Patent Publication No. 1-53672.

[0011] The pulmonary circulation improving agent of the present invention has the dilating action selective to the pulmonary blood vessels, and is effective as an agent for curing diseases which cause an increase in the pulmonary vascular resistance. The agent also exhibits effectiveness for an increase in the pulmonary vascular resistance which occurs after surgery. Furthermore, the agent selectively decreases the pulmonary vascular resistance as the right heart afterload, and is thus effective as an agent for curing right heart failure.

[0012] Diseases which cause an increase in the pulmonary vascular resistance include congenital heart diseases such as Eisenmenger syndrome; diseases causing hypoxemia, such as adult respiratory distress syndrome (ARDS); diseases causing an organic change, such as pulmonary fibrosis; thrombotic diseases of the pulmonary blood vessels, such as pulmonary embolism; pulmonary hypertension such as primary pulmonary hypertension, pulmonary hypertension as a complication of collagen disease; and the like.

[0013] The present invention also provides the pulmonary circulation improving method comprising administering a patient suffering from an increase in the pulmonary vascular resistance with an agent containing as an active ingredient the above prostaglandin I derivative(s). As an administration method, a prostaglandin I derivative is administered 1 to 3 times a day in a dose of 0.01 to 100 mg/adult.

[0014] Although the pulmonary circulation improving agent of the present invention may contain at least one prostaglandin I derivative, the agent can also be orally administered in the form of a solid containing the additives below.

[0015] Examples of such additives include an excipient such as starch, lactose, sucrose, glucose, mannitol, calcium carbonate, calcium sulfate, or the like; a binder such as starch, dextrin, gum arabic, tragacanth, methyl cellulose, gelatin, polyvinyl pyrrolidone, polyvinyl alcohol, or the like; a disintegrator such as starch, polyvinyl pyrrolidone, crystalline cellulose, or the like; a lubricant such as magnesium stearate, talc, or the like; a colorant; a flavor; and the like.

[0016] The prostaglandin I derivatives of the present invention can be used in various forms. Examples of the forms include generally used forms such as a tablet, a sugar-coated tablet, a powder, granules, a troche capsule, a pill, a syrup, and the like.

[0017] The prostaglandin I derivatives may be parenterally administered in the form of a sterilized solution, and another solute such as sodium chloride, glucose, or the like can also be used in an amount sufficient for making the solution isotonic.

[0018] The pulmonary circulation improving agent of the present invention can be applied to the above oral formulations and a variety of other parenteral formulations such as various injections, suppositories, and the like.

[Examples]

[0019] Although the present invention is described in detail below with reference to an example, the present invention is not limited to this example.

Example 1

[0020] Test of comparison with other vasodilating agents in dog:

[0021] A thromboxane receptor agonist U-46619 was continuously injected into anesthetized dogs in a dose of 0.3 μg/kg/min to increase the pulmonary arterial pressure. Beraprost sodium (100, 300 ng/kg/min) and prostaglandin E_1 (0.3, 1 μg/kg/min), nitroglycerin (3, 10 μg/kg/min) and nifedipine (0.3, 1 μg/kg/min) were continuously intravenously administered in a dose causing the same degree of decrease in blood pressure as beraprost sodium to examine decreases in the pulmonary arterial pressure and the systemic blood pressure and decreases in the pulmonary vascular resistance and the systemic vascular resistance. Fig. 1 shows changes in the pulmonary arterial pressure/systemic blood pressure ratio, and Fig. 2 shows changes in the pulmonary vascular resistance/systemic vascular resistance ratio. In Figs. 1 and 2, BPS represents beraprost sodium, PGE_1 represents prostaglandin E_1, GTN represents nitroglycerin, and NIF represents nifedipine. In each of the figures, the ratio on the ordinate are based on a value of 1 before administration of medicines. Marks "*" and "**" represent comparisons with values before administration of medicines with $p < 0.05$ and 0.01, respectively (paired t-test).

[0022] Both figures indicate that beraprost sodium significantly decreases the pulmonary arterial pressure/systemic blood pressure ratio and the pulmonary vascular resistance/systemic vascular resistance ratio, and selectively dilates the pulmonary blood vessels. On the other hand, such an action was not observed in prostaglandin E_1, nitroglycerin and nifedipine.

Industrial Applicability

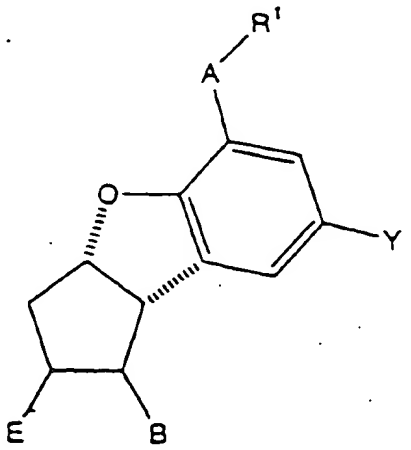
[0023] The pulmonary circulation improving agent of the present invention has the dilating action selective to the pulmonary blood vessels, and the present invention provides a pulmonary circulation improving agent having excellent effectiveness and practicability.

Claims

1. A pulmonary circulation improving agent containing a prostaglandin I derivative as an active component.

2. The pulmonary circulation improving agent according to Claim 1, wherein the prostaglandin I derivative is a prostaglandin I_2 derivative.

3. The pulmonary circulation improving agent according to Claim 1, wherein the prostaglandin I derivative is a 4,8-inter-m-phenylene prostaglandin I_2 derivative or a pharmacologically acceptable salt thereof represented by the following formula (I):



(I)

[wherein R^1 is the following:

(A) $COOR^2$ wherein R^2 is:

1) hydrogen or pharmacologically acceptable cation;
2) straight chain alkyl having 1 to 12 carbon atoms or branched alkyl having 3 to 14 carbon atoms;
3) $-Z-R^3$

wherein Z is a valence bond or straight chain or branched alkylene represented by C_tH_{2t} wherein t represents an integer of 1 to 6, and R^3 is cycloalkyl having 3 to 12 carbon atoms or substituted cycloalkyl having 3 to 12 carbon atoms and substituted by 1 to 3 R^4 groups which are each hydrogen or alkyl having 1 to 5 carbon atoms;

4) $-(CH_2CH_2O)_nCH_3$
wherein n is an integer of 1 to 5;
5) $-Z-Ar^1$
wherein Z is defined as the same as the above, and Ar^1 is phenyl, α-naphthyl, β-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, α-furyl, β-furyl, α-thienyl, β-thienyl or substituted phenyl (wherein the substituent is at least one chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl, phenoxy, p-acetoamidobenzamido, $-CH=N-NH-C(=O)-NH_2$, $-NH-C(=O)-Ph$, $-NH-C(=O)-CH_3$ or $-NH-C(=O)-NH_2$);
6) $-C_tH_{2t}COOR^4$
wherein C_tH_{2t} and R^4 are defined as the same as the above;
7) $-C_tH_{2t}N(R^4)_2$
wherein C_tH_{2t} and R^4 are defined as the same as the above;
8) $-CH(R^5)-C(=O)-R^6$
wherein R^5 is hydrogen or benzoyl, and R^6 is phenyl, p-bromophenyl, p-chlorophenyl, p-biphenyl, p-nitrophenyl, p-benzamidophenyl, or 2-naphthyl;
9) $-C_pH_{2p}-W-R^7$
wherein W is $-CH=CH-$, $-CH=CR^7$ or $-C\equiv C-$, and R^7 is hydrogen or straight chain or branched alkyl or aralkyl having 1 to 30 carbon atoms, and p is an integer of 1 to 5; or
10) $-CH(CH_2OR^8)_2$
wherein R^8 is alkyl or acyl having 1 to 30 carbon atoms;

(B) $-CH_2OH$;
(C) $-C(=O)N(R^9)_2$
wherein R^9 is hydrogen, straight chain alkyl having 1 to 12 carbon atoms, branched alkyl having 3 to 12 carbon atoms, cycloalkyl having 3 to 12 carbon atoms, cycloalkylalkylene having 4 to 13 carbon atoms, phenyl, substituted phenyl (wherein the substituent is defined as the same as (A) 5)), aralkyl having 7 to 12 carbon atoms, or $-SO_2R^{10}$ wherein R^{10} is alkyl having 1 to 10 carbon atoms, cycloalkyl having 3 to 12 carbon atoms, phenyl, substituted phenyl (the substitutent is defined as the same as the above in (A) 5)), or aralkyl having 7 to 12 carbon atoms, and two R^9 groups may be the same or different, and when one of the R^9 groups is $-SO_2R^{10}$, the other R^9 is not $-SO_2R^{10}$; or
(D) $-CH_2OTHP$ (THP is a tetrahydropyranyl group).

A is the following:

1) $-(CH_2)_m-$,
2) $-CH=CH-CH_2-$;
3) $-CH_2-CH=CH-$;
4) $-CH_2-O-CH_2-$;
5) $-CH=CH-$;
6) $-O-CH_2-$, or
7) $-C\equiv C-$;
wherein m represents an integer of 1 to 3.

Y is hydrogen, alkyl having 1 to 4 carbon atoms, chlorine, bromine, fluorine, formyl, methoxy or nitro;
B is $-X-C(R^{11})(R^{12})OR^{13}$
wherein R^{11} is hydrogen, alkyl having 1 to 4 carbon atoms; R^{13} is hydrogen, acyl having 1 to 14 carbon atoms, aroyl having 6 to 15 carbon atoms, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, or t-butyl; X is the following:

1) $-CH_2-CH_2-$,
2) $-CH=CH-$; or
3) $-C\equiv C-$; and

R^{12} is the following:

1) straight chain alkyl having 1 to 12 carbon atoms, or branched alkyl having 3 to 14 carbon atoms;
2) -Z-Ar^2
wherein Z is the defined as the same as the above, and Ar^2 represents phenyl, α-naphthyl, β-naphthyl, or phenyl substituted by at least one chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy;
3) -$C_tH_{2t}OR^{14}$
wherein C_tH_{2t} is defined as the same as the above, and R^{14} represents straight chain alkyl having 1 to 6 carbon atoms, branched alkyl having 3 to 6 carbon atoms, phenyl, phenyl substituted by at last one chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy, cyclopentyl, cyclohexyl, or cyclopentyl or cyclohexyl substituted by 1 to 4 straight chain alkyl groups having 1 to 4 carbon atoms;
4) -Z-R^3
wherein Z and R^3 are defined as the same as the above;
5) -C_tH_{2t}-CH=C(R^{15})R^{16}
wherein C_tH_{2t} is defined as the same as the above, and R^{15} and R^{16} each represent hydrogen, methyl, ethyl, propyl, or butyl; or
6) -C_uH_{2u}-C≡C-R^{17}
wherein u is an integer of 1 to 7, C_uH_{2u} represents straight chain or branched alkylene, and R^{17} represents straight chain alkyl having 1 to 6 carbon atoms;

E is hydrogen or -OR^{18}
wherein R^{18} represents acyl having 1 to 12 carbon atoms, aroyl having 7 to 15 carbon atoms, or R^2 (wherein R^2 is defined as the same as the above); and
the formula represents the d, l or dl form].

4. The pulmonary circulation improving agent according to Claim 1, wherein the prostaglandin I derivative is beraprost or a salt thereof.

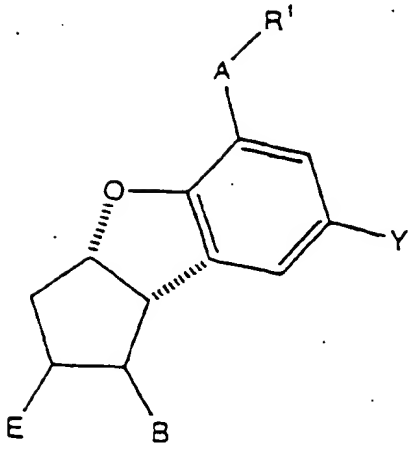
5. The pulmonary circulation improving agent according to Claim 1, wherein the prostaglandin I derivative is ataprost, iloprost, clinprost, ciprostene, naxaprostene, taprostene, cicaprost, pimilprost, CH-169, or CS570.

6. A pulmonary circulation improving method comprising administering a patient suffering from an increase in the pulmonary vascular resistance with an agent containing a prostaglandin I derivative as an active component.

7. The pulmonary circulation improving method according to Claim 6, comprising administering the prostaglandin I derivative 1 to 3 times a day in a dose of 0.01 to 100 mg/adult.

8. The pulmonary circulation improving method according to Claim 6, wherein the prostaglandin I derivative is a prostaglandin I_2 derivative.

9. The pulmonary circulation improving method according to Claim 6, wherein the prostaglandin I derivative is a 4,8-inter-m-phenylene prostaglandin I_2 derivative or a pharmacologically acceptable salt thereof represented by the following formula (I).



(I)

[wherein R^1 is the following:

(A) $COOR^2$ wherein R^2 is:

1) hydrogen or pharmacologically acceptable cation;
2) straight chain alkyl having a carbon number of 1 to 12 or branched alkyl having 3 to 14 carbon atoms;
3) $-Z-R^3$
wherein Z is a valence bond or straight chain or branched alkylene represented by C_tH_{2t} wherein t represents an integer of 1 to 6, and R^3 is cycloalkyl having 3 to 12 carbon atoms or substituted cycloalkyl having 3 to 12 carbon atoms and substituted by 1 to 3 R^4 groups which are each hydrogen or alkyl having 1 to 5 carbon atoms;
4) $-(CH_2CH_2O)_nCH_3$
wherein n is an integer of 1 to 5;
5) $-Z-Ar^1$
wherein Z is defined as the same as the above, and Ar^1 is phenyl, α-naphthyl, β-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, α-furyl, β-furyl, α-thienyl, β-thienyl or substituted phenyl (wherein the substituent is at least one chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl, phenoxy, p-acetoamidobenzamido, $-CH=N-NH-C(=O)-NH_2$, $-NH-C(=O)-Ph$, $-NH-C(=O)-CH_3$ or $-NH-C(=O)-NH_2$);
6) $-C_tH_{2t}COOR^4$
wherein C_tH_{2t} and R^4 are defined as the same as the above;
7) $-C_tH_{2t}N(R^4)_2$
wherein C_tH_{2t} and R^4 are defined as the same as the above;
8) $-CH(R^5)-C(=O)-R^6$
wherein R^5 is hydrogen or benzoyl, and R^6 is phenyl, p-bromophenyl, p-chlorophenyl, p-biphenyl, p-nitrophenyl, p-benzamidopnenyl, or 2-naphthyl.
9) $-C_pH_{2p}-W-R^7$
wherein W is $-CH=CH-$, $-CH=CR^7$ or $-C\equiv C-$, and R^7 is hydrogen or straight chain or branched alkyl or aralkyl having 1 to 30 carbon atoms, and p is an integer of 1 to 5; or
10) $-CH(CH_2OR^8)_2$
wherein R^8 is alkyl or acyl having 1 to 30 carbon atoms.

(B) $-CH_2OH$;
(C) $-C(=O)N(R^9)_2$
wherein R^9 is hydrogen, straight chain alkyl having 1 to 12 carbon atoms, branched alkyl having 3 to 12 carbon atoms, cycloalkyl having 3 to 12 carbon atoms, cycloalkylalkylene having 4 to 13 carbon atoms, phenyl, substituted phenyl (wherein the substituent is defined as the same as (A) 5)), aralkyl having 7 to 12 carbon atoms, or $-SO_2R^{10}$ wherein R^{10} is alkyl having 1 to 10 carbon atoms, cycloalkyl having 3 to 12 carbon atoms, phenyl, substituted phenyl (the substitutent is defined as the same as the above in (A) 5)), or aralkyl having 7 to 12 car-

bon atoms, and two R^9 groups may be the same or different, and when one of the R^9 groups is $-SO_2R^{10}$, the other R^9 is not $-SO_2R^{10}$; or

(D) $-CH_2OTHP$ (THP is a tetrahydropyranyl group);

A is the following:

1) $-(CH_2)_m-$;
2) $-CH=CH-CH_2-$;
3) $-CH_2-CH=CH-$;
4) $-CH_2-O-CH_2-$;
5) $-CH=CH-$;
6) $-O-CH_2-$; or
7) $-C\equiv C-$;
wherein m represents an integer of 1 to 3;

Y is hydrogen, alkyl having 1 to 4 carbon atoms, chlorine, bromine, fluorine, formyl, methoxy or nitro;
B is $-X-C(R^{11})(R^{12})OR^{13}$
wherein R^{11} is hydrogen, alkyl having 1 to 4 carbon atoms; R^{13} is hydrogen, acyl having 1 to 14 carbon atoms, aroyl having 6 to 15 carbon atoms, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, or t-butyl; X is the following:

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R^{12} is the following:

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wherein Z is the defined as the same as the above, and Ar^2 represents phenyl, α-naphthyl, β-naphthyl, or phenyl substituted by at least one chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy;
3) $-C_tH_{2t}OR^{14}$
wherein C_tH_{2t} is defined as the same as the above, and R^{14} represents straight chain alkyl having 1 to 6 carbon atoms, branched alkyl having 3 to 6 carbon atoms, phenyl, phenyl substituted by at last one chlorine, bromine, fluorine, iodine, trifluoromethyl, alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy, cyclopentyl, cyclohexyl, or cyclopentyl or cyclohexyl substituted by 1 to 4 straight chain alkyl groups having 1 to 4 carbon atoms;
4) $-Z-R^3$
wherein Z and R^3 are defined as the same as the above;
5) $-C_tH_{2t}-CH=C(R^{15})R^{16}$
wherein C_tH_{2t} is defined as the same as the above, and R^{15} and R^{16} each represent hydrogen, methyl, ethyl, propyl, or butyl; or
6) $-C_uH_{2u}-C\equiv C-R^{17}$
wherein u is an integer of 1 to 7, C_uH_{2u} represents straight chain or branched alkylene, and R^{17} represents straight chain alkyl having 1 to 6 carbon atoms.

E is hydrogen or $-OR^{18}$
wherein R^{18} represents acyl having 1 to 12 carbon atoms, aroyl having 7 to 15 carbon atoms, or R^2 (wherein R^2 is defined as the same as the above); and
the formula represents the d, l or dl form].

10. The pulmonary circulation improving method according to Claim 6, wherein the prostaglandin I derivative is beraprost or a salt thereof.

11. The pulmonary circulation improving method according to Claim 6, wherein the prostaglandin I derivative is ataprost, iloprost, clinprost, ciprostene, naxaprostene, taprostene, cicaprost, pimilprost, CH-169, or CS570.

FIG. 1

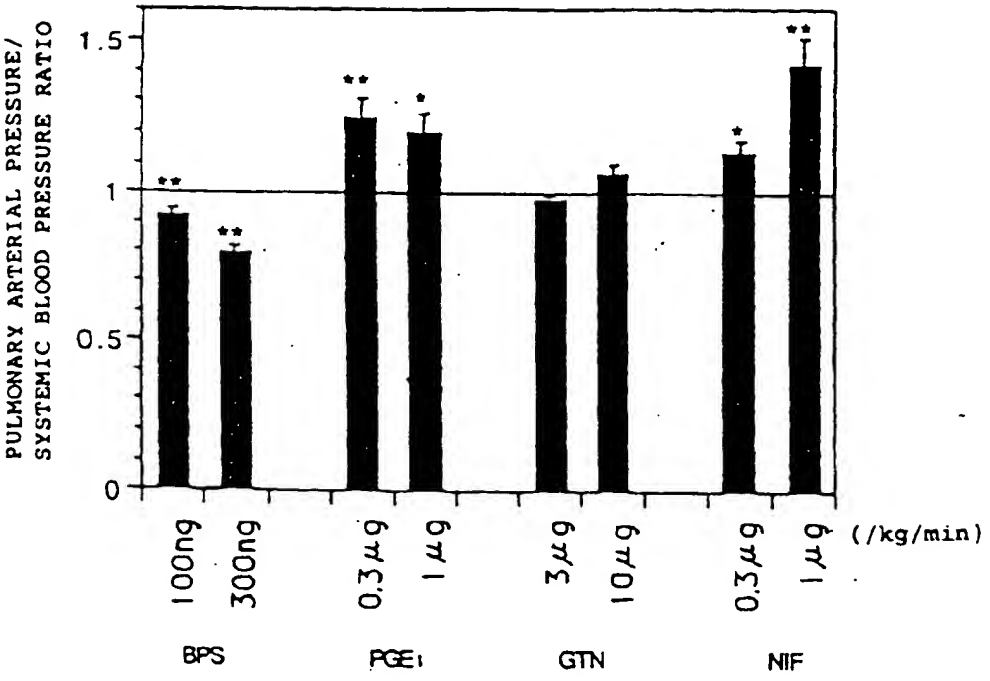
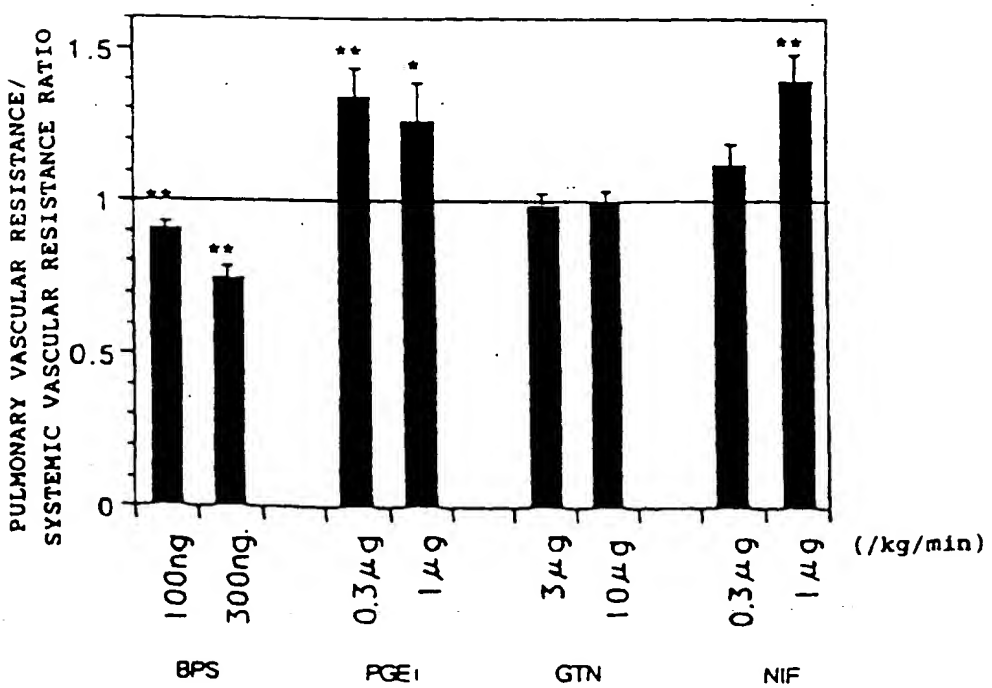

PULMONARY ARTERIAL PRESSURE/
SYSTEMIC BLOOD PRESSURE RATIO
1.5
1
0.5
0
100ng
300ng
0.3μg
1μg
3μg
10μg
0.3μg
1μg
(/kg/min)
BPS
PGE1
GTN
NIF

FIG. 2


PULMONARY VASCULAR RESISTANCE/
SYSTEMIC VASCULAR RESISTANCE RATIO
1.5
1
0.5
0
100ng
300ng
0.3μg
1μg
3μg
10μg
0.3μg
1μg
(/kg/min)
BPS
PGE1
GTN
NIF

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/00801

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] A61K31/557

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] A61K31/557

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP, 58-124778, A (Toray Industries, Inc.), July 25, 1983 (25. 07. 83), Claims ; page 12, upper left column, lines 8 to 15 & EP, 84856, A1 & US, 4474802, A	1-5
X	UENO, Yuji et al., "EFFECT OF BERAPROST SODIUM, A STABLE PROSTACYCLIN ANALOGUE, ON PULMONARY THROMBOEMBOLISM IN MICE", Thrombosis Research, Vol. 77, No. 2, (1995), p.193-198	1-5
X	JP, 60-36477, A (Schering AG.), February 25, 1985 (25. 02. 85), Claims ; page 7, lower right column, lines 5 to 20 & EP, 130142, A1 & US, 4894391, A	1, 2
X	JP, 57-206679, A (Schering AG.), December 18, 1982 (18. 12. 82), Claims ; page 6, upper left column, line 23 to upper right column, line 18 & EP, 51558, A1 & US, 4364951, A	1, 2

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
May 15, 1998 (15. 05. 98)	May 26, 1998 (26. 05. 98)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/00801

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [x] Claims Nos.: 6-11

because they relate to subject matter not required to be searched by this Authority, namely:

Claims 6 to 11 pertain to methods for treatment of the human body by surgery or therapy.

2. [ ] Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1 [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3 [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4 [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)